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CURRENT SCENARIO ON USE OF ISOTRETINOIN IN VARIOUS FORMS OF ACNE

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BACKGROUND

Acne is estimated to affect 9.4% of the population globally in which it is commonly seen in post pubescent teens, predominantly in males.[1] Across gender females (56%) showed significantly higher prevalence than males (51.6%), alongside males showing higher incidence than females in onset of disease at younger age. In case of mild acne condition females significantly showed higher prevalence than males, while in case of moderate and severe condition it was observed to be common in males than females.[2] To paramount the prevalence and severity of acne vulgaris in adolescents, a cross-sectional, study was performed that was community-based. In it, 1,002 people with an age of 16±0.9 years were volunteered. In the study the prevalence rate was 93.3; 94.4% and 92.0% for boys and girls respectively among which 14% of the members had moderate to severe acne. Here, the prevalence of moderate to severe acne was 19.9% in those with and 9.8% in those without a family history of acne (P<0.0005; OR: 2.3).[3] According to a past study, the prevalence of facial acne in 15–25 years of age group was 91.3% (95% CI 88.9–93.7). Another study was done to exhibit the occurrence of acne due to increased sebum production, shown 91.3%, of the prevalence rate.[4] Throughout the age from third decade the etiology of acne appear to be changed in adulthood. The prevalence rate is higher in post-adolescent women, in distinction to a high prevalence in adolescent male.[5] As isotretinoin has teratogenic effect, so female patients on the therapy of isotretinoin that are clinged to multiple contraception mehods should strictly be forewarned not to be pregnant. In a cohort study, it has been demonstrated that out of 8609 women, 210 were pregnant during the therapeutic regimen of isotretinoin: 68 were pregnant at the time when they started their therapy on isotretinoin (32%), 90 became pregnant at that period when they were taking isotretinoin (43%) and 52 became pregnant on

discontinuation of isotretinoin (25%).[6] The isotretinoin therapy within the first trimester have been related with congenital malformations.[7]

KEYWORDS: Isotretinoin, teratogenic, acne, retinoids, iPLEDGE.

INTRODUCTION

Acne is a common skin disorder caused by abnormal hyperkeratinization and over-production of sebum by the sebaceous gland.[8] The word acne is derived from Greek word acme which means prime of life. It is considered to be a benign, self limiting condition or a pleomorphic disorder that barefaces at any time during life but it most commonly presents between ages of 12-24, which affects of 85% of population.[9] The appendages to acne includes psychological effects like anxiety, depression, low self esteem and self confidence, discomfiture, shame or social inhibitions sometimes leading to suicidal ideation.[10] It is a multifactorial disease affecting the pilosebaceous follicles that arises due to 4 pathogenic factors: sebum production, follicular hyperkeratinization, microbial colonization of the pilosebaceous unit by Propionibacterium acnes and the release of inflammatory mediators into the follicle.[11] Acne is known to posess disease course including pathological skin surface features like increased sebum excretion, alteration of lipid and oxidant/antioxidant ratio.[12] A higher fatty acid level in sebum secretion leads to higher prevalence of acne which is demonstrated by a study in twins having higher fatty acid level in wax esters with acne than in twins without acne.[13] Acne patients have characteristic of skin structure with low levels of linoleic acid in surface lipids.[14] According to the recent evidences, amongst the factors that influence the course of acne like sebum concentration and skin surface composition, Propionibacterium acnes has also greatly affected the emergence of the condition. Modernness in pathophysiology of acne is that inflammatory condition is more often seen than hyperkeratinization. The inflammatory course of acne is due to the activation of toll-like receptor (TLR) on the membranes of inflammatory cells. Sebum production by the sebaceous gland that is a neuroendocrine inflammatory organ gets partly regulated by Peroxisome proliferator-activated receptors. The inflammatory mediators can stimulate the production of oxidized lipids in sebum. Matrix metalloproteinases (MMPs) present in sebum get decreased with the recovery of acne lesions.[15] Various grading systems are there for the evaluation of severity of acne. Tutakne et al., in 2003, suggested that acne be graded as 1 to 4 depending on the severity of skin lesions.[16] The clinical presentation of acne differs according to the severity in different patients. Indian authors gave a simple grading system for acne vulgaris as follows.

Grade 1: Comedones, occasional papules.

Grade 2: Papules, comedones, few pustules.

Grade 3: Predominant pustules, nodules, abscesses.

Grade 4: Mainly cysts, abscesses, widespread scarring.[17]

According to American Academy of Dermatology a Consensus Conference classified acne severity.[18] According to this consensus, the grading system of acne vulgaris includes.

1. Mild acne, the presence of comedones as well as few to several papules-pustules;
2. Moderate acne, differentiated by several papules, pustules and few to several nodules;
3. Severe acne, characterized by numerous or extensive papules-pustules, or both, along with many nodules; and
4. Very severe forms of acne, including the most destructive conditions of the disease, such as acne conglobata, acne fulminans and the follicular occlusion triad.[19]

With ongoing research on pathophysiology of acne, new therapeutic indication has been found out. Severity of acne influence the type of therapy that should be provided for the disease. Among oral antibiotics, hormonal therapy and isotretinoin, the treatment is imparted depending upon the condition of the patient.[20] A group of dermatologists with clinical proficiency in acne vulgaris founded a Global Alliance to Improve Outcomes in Acne Group. The Global Alliance assures the rational use of antimicrobials in therapies. Besides immense efforts of the professionals the resistance to the antimicrobials still persist.[21] The Pathophysiological approach should direct the therapy of acne which can include both mono therapy as well as combination therapy with isotretinoin depending upon the seriousness of the disease that targets at major mechanisms of acne pathogenesis.[22]

ISOTRETINOIN IN THERAPY OF ACNE

Isotretinoin is a retinoid or vitamin A derivative. It is approved by FDA and reviewed by dermatologists as potent drug for the treatment of severe recalcitrant nodular acne to which in which other antibiotics stop responding. In many of the randomized, double blinded clinical studies the efficacy of systemic isotretinoin therapy has been signified. Isotretinoin is evident in the use of the severe forms of acne, particularly severe recalcitrant nodular acne or acne which has proven contrary to other forms of therapy. The severity of the disease can be estimated by the physical and psychological influence of the disease on the patient.[23]

THERAPEUTIC INDICATION OF ISOTRETINOIN

Retinoids are utilized in the treatment for acne vulgaris because they act on the excessive keratinization in the follicles of the skin in the patients of acne.[24] In case of adverse effects like cheilitis and skin dryness, the grading system used was as follows.

Mild: Emollients were adequate for treatment.

Moderate: The Intermittent topical steroid was requisite for the treatment.

Severe: A potent steroidal ointment and oral antibiotics, together with antiseptics, were mandatory.[25]

There was an inconsistent recurrence as an increase in the severity of acne grade that exists during follow-up, in comparison with that at the end of treatment. The oral isotretinoin was started in.

1) Acne with a moderate or high grade.
2) Lack of response to common drugs, including oral antibiotics in grade I or II acne; and
3) Dysmorphophobia in patients with grade I or II acne.

Unresponsive to conventional therapy, those patients with severe acne are recommended to be administered a low dose isotretinoin i.e. 0.5 to 1.0 mg/kg/day but there is a insufficiency of safety and efficacy data related to the side effects at this dose.[26] Low-dose of isotretinoin was found to be similar as higher doses in aspects of efficacy for treating acne with severe clinical presentation.[27]

RECOMMENDED SAFE HIGH DOSE OF ISOTRETINOIN

When the three-year study period was there into a study 10 patients (12.5%) progressed a relapse that required the therapy of isotretinoin into the treatment remarkable advancement in QOL lets to preserve self-perception and the symptoms are observed after isotretinoin therapy. The dose of Isotretinoin prescribed by the physician is 1.5 mg/kg/day or more than that for 5-6 months [cumulative total dose of 290 mg/kg] is safe and effective in comparison with that of the current standard dosing practices in severe nodulocystic acne.[28] In some of the studies dose of isotretinoin was found to be 120 to 150 mg/kg which lead to a decrease in the probability of relapse and retrial. There are some newer studies that demonstrated lower rates of relapse and retrial with higher doses.[29] A 2011 study demonstrated that high dose of

isotretinoin is a standard-dose therapy that is safe and effective for the treatment of acne which is advantageous to prevent the relapse rate in acne. Although the recommended dose of the drug is 120 to 150 mg/kg, more than 20% of patients experience a relapse within 2 years so, a medical management is needed for such patients.[30]

OPTIMUM SAFE LOW DOSE OF ISOTRETINOIN

As recommended in the early stage of the presentation in patients with moderate to severe acne, 69% of resolution was in the acne scars. The patients with pre-existing scarring experienced 91% of success rate at a dose of 120 mg/kg with fewer adverse effects.[31] The effect of low-dose isotretinoin seems to be same as that of higher doses for resolving acne and based on this newer evidence, the recommended therapy of isotretinoin was observed to be 10–20 mg/day, 50% of patients reported less severe adverse effects.[32] The duration of isotretinoin therapy is currently based on the calculated aggregate dose. The relapse of bacteria was observed in one to two years after a single 16-week course of low dose of isotretinoin. When the aggregate dose reached 120 – 140 mg/kg a long-term response from isotretinoin was procured.[33]

COMPARISON OF HIGH DOSE AND LOW DOSE ISOTRETINOIN

After one month of systemic isotretinoin treatment the rate of conjunctival S. aureus colonization was independent of the dose of isotretinoin but there was increase in the incidence of eye dryness in some of the patients.[34] After high doses of isotretinoin (greater than 2 mg/kg/day) more chances of skeletal toxicity arised and musculoskeletal toxicity was more often found out in patients with low dose of isotretinoin (0.5 mg/kg/day) used in the treatment of severe acne. Musculoskeletal toxicity as shown by Radiographs associated with patients on higher dose, 12% showed minor changes such as spinal hyperostoses and calcaneal hyperostoses as compared to patients on low doses of isotretinoin.[35] The relapse rate of the lower-dose treatment group (<220 mg/kg), and higher- dose treatment group were 47.4% and 26.9% respectively. Adverse effects like retinoid dermatitis, cheilitis and xerosis were experienced by 100% of the patients significantly more common in the high-dose treatment group i.e 53.8% vs 31.6%.[36]

RECENT UPDATES IN SAFETY

As discovered by the recent evidence in the aspect of efficacy of Isotretinoin, it is best prescribed at lower daily dose, (eg., 10-20mg daily) and few adverse effects of Isotretinoin are obtained as lower doses appear to be effective as higher doses.[37] Due to the high degree

of adverse effects, Isotretinoin should be contemplated only in the patients unresponsive to other therapy. In the women who are pregnant or who may become pregnant or breastfeeding, in case of hepatic insufficiency, hypervitaminosis A and severe hyperlipidaemia the therapy of Isotretinoin is contraindicated.[38] Side-effects such as mood changes, depression, and suicidal ideation have been reported in patients on therapy of isotretinoin.[39] A recent study was conducted that resulted into the acne clearance rates between 92 – 95% in people taking isotretinoin 20 mg per day for six months (equivalent to 0.28 mg/kg per day, with a cumulative dose of 52 mg/kg). This is comparable to the rate of clearance achieved with a traditional regimen of 0.5 – 1 mg/kg per day, with a cumulative dose of 150 mg/kg.[40] Oral isotretinoin counteracts the pathogenic factors that contribute to the development of acne vulgaris.[41] In a study it was signified that the acne scores ranged from 3.11 ± 0.49 to 0.65 ± 0.62 (P = <0.001) at the end of 12 weeks. A low acne score continued was obtained at the end of 6 months (0.5 ± 0.52, P = <0.001). A decrease in depression is shown by the HRSD scores from 3.89 ± 4.9 to 0.45 ± 1.12 (P <0.001) at the end of 3 months and further reduction at the end of 6 months at 0.18 ± 0.51 (P = <0.001) Before the isotretinoin therapy was started the scoring for depression was higher and the scoring was found to decrease steadily during the treatment period and the reduction was found to be significant at the end of three months of therapy. No worsening of the scores of the patients or suicidal thoughts were developed during the 6 months of follow up period. Cheilitis was found the common adverse effect. A clinical improvement was observed significantly on the administration of oral isotretinoin in moderate to severe acne and thus a decrease in depression scores is obtained.[42] In 20% of patients Isotretinoin emerged with some mild rheumatologic side effects like musculoskeletal pain and arthralgias which usually disappear on stopping the treatment. Arthritis is one of the unusual rheumatologic side effect of isotretinoin. An association between sacroiliitis and the use of Isotretinoin has been well illustrated in some of the studies. Isotretinoin due to its detergent-like properties leads to the solubilization of the liposomal membrane results in arthritis by the destruction of synovial cells. Sacroiliac joint involvement has been reported to occur in approximately 21% of patients in which arthritis accompanies acne. Sulfasalazine, a disease-modifying anti-rheumatic drug can be used in such patients.[43] The patients who were taking the drug as a long-term therapy, suffering from ossification disorders of the spine and extra-spinal locations, such as the wrists, elbows, ankles, hips and calcaneal regions that was linked to lamellar icthyosis in some patients. These patients manifested ossification disorder resembling diffuse idiopathic skeletal hyperostosis, but all were younger, had generally thinner and more sclerotic lesions, and showed a more rapid progression of their

disease than do patients with the typical idiopathic variety.[44] There are several etiologic factors contributing to acne development in which oral isotretinoin has revolutionized the treatment of acne.[45] It has been reported before that the chance of teratogenicity and depression prevails from isotretinoin usage, a program named iPLEDGE presented isotretinoin as a very dangerous regimen.[46] During the 5-year study period 1419 subjects had been exposed to Isotretinoin who were serving compulsory military service at the age range of 18 to 22 years old with the majority being male (67%). There were two groups, in one of them the acne was treated with Isotretinoin who were served by a mental health professional, the rate was higher 17.2% (245/1419) compared to 12.5% (138/1102) of the control (psoriasis) group. There were some behavioral problems observed in some prisoners in a military jail that there was no difference in the frequency of events of abandonment between the index group and controls. Among the subjects of the group in which Isotretinoin was the drug of choice 99 subjects had served time in jail (6.9%) and 9 subjects agonized episodes of desertion (0.6%). A recent work by Bremner and colleagues reported that Isotretinoin treatment was associated with decreased brain metabolism in the orbitofrontal cortex, a brain area known to mediate symptoms of depression. The exclusion of conscripts with a history of major depression from the army may have detracted from the true effect size of exposure to Isotretinoin.[47] Early intervention with isotretinoin has the potential to not only minimize physical and psychological impact, but lessen the financial burden. Pregnancy prevention should be strongly emphasized at every point during the course of treatment and iPLEDGE should be utilized.[48] Between March 1, 2004 and February 29, 2008, a total of 8344 FCBP received 9912 treatment courses of isotretinoin. There were 5788 treatment courses during the SMART program and 4124 treatment courses during the iPLEDGE program. After iPLEDGE implementation, FCBP were more likely to have received a prior course of isotretinoin, more likely to have received previous prescription acne medications and had longer treatment courses. It turned out to be evident that the iPLEDGE program significantly decreased the rate of fetal exposures to isotretinoin in FCBP. Without understanding these issues, further increase in patient barriers to isotretinoin therapy in future RMPs will likely be ineffective in reducing pregnancy rates in this patient population.[49] On the administration of isotretinoin, the amount of oil secreted by the sebaceous glands is diminished. Under the iPLEDGE program the isotretinoin is readily made accessible. The selling of isotretinoin outside of the iPLEDGE program breaches the regulations of the U.S. Food and Drug Administration to promote the secure use of this medication.[50]

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